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David L. Parker

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lopez-Berestein et al.

Serial No.: 09/982,113

Filed: October 17, 2001

For: A METHOD TO INCORPORATE N-(4-HYDROXYPHENYL) RETINAMIDE IN LIPOSOMES

Group Art Unit: 1615

Examiner: Kishore, Gollamudi S.

Atty. Dkt. No.: UTSC:660US

REPLY BRIEF

M.S. APPEAL BRIEF - PATENTS
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences to address matters raised in the Examiner's Answer dated July 28, 2005 making the present Reply Brief due on September 28, 2005. It is believe that no fee is due in connection with the filing of this Reply Brief; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed material, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski L.L.P. Account No.: 50-

1212/UTSC:660US. Appellants have enclosed herewith a request for oral hearing and the required fee for that request.

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APPELLANTS' REPLY

Appellants contend that the Examiner's Answer in no way explains remedies the shortcomings in the rejections which, as explained in the opening brief, fail to be based on substantial evidence of *prima facie* obviousness.

Claim 138

With respect to claim 138, we would first reiterate the teachings of the subject specification: that to prepare a 4-HPR liposome "encapsulated in a lipid material, *wherein the lipid material comprises dimyristoyl phosphotidylcholine (DMPC) and water*" as set forth in claim 138 and described in the specification, one includes the water in the organic solvent used to prepare the liposome in order to get the water into the lipid component. See, for example, Specification at page 83, lines 13-16, and particularly Table 2. Table 2 on page 83 demonstrates that when water is included in the organic alcohol solvent a surprising increase in incorporation efficiency is seen, as compared to using the solvent alone with no water added. Note in particular that in *both* cases (*t*-butanol without water, and *t*-butanol with water) saline was used to resuspend the already formed liposomes. Specification, page 83, lines 19-20.

The Answer responds to the foregoing by first stating:

> These arguments are not found to be persuasive. First of all, as pointed out before, liposomes are bilayer structures formed by specific orientation of the phospholipids when hydrated with water or aqueous medium. Dissolving the phospholipids in an organic solvent, removing the organic solvent, and adding an aqueous medium and either vortexing or sonicating to form liposomes is a conventional method of preparation of liposomes. ... Without an aqueous medium **liposomal structures do not form at all.**

Answer, paragraph bridging pages 4 and 5 (emphasis in original).

In response, Appellants would again note that the inclusion of water in the organic alcohol used to form the liposomes in the present invention clearly had a substantial effect on the

incorporation efficiency. More importantly, there was an internal control in the Appellants' examples in that both the liposomes made with t-butanol alone and those made t-butanol + water were resuspended with aqueous saline. If the Examiner were correct in his implication that *resuspension* of liposomes in aqueous saline interjected water into the lipid bilayer, one would expect there to be no difference between including water in the t-butanol as compared to leaving the water out. The scientific evidence suggests that the Examiner is incorrect in this assumption.

Further, Appellants disagree with the Examiner's unsupported statements that "without an aqueous medium liposomal structures do not form at all." As with most of the scientific statements made by the Examiner in his Answer, this statement is made without any reference to the prior art or support from any other substantive text and thus is not supported by *any* evidence, substantial or otherwise. Furthermore, it is submitted that this unsupported statement is incorrect. The description in the present specification at pages 32-33 referred to by the Examiner states that water IS included in the t-butanol (in contrast to Mehta *et al.*, where water was not included in the t-butanol), and that the lipid bilayers are actually formed during the lyophilization phase when the t-butanol is removed, not, as the Examiner alleges, during the resuspension stage. For example, at the bottom of page 32 and top of page 33 it is noted that the drug is mixed with the lipids along with the t-butanol + water and THIS mixture is lyophilized to form the liposomes. Then, "[w]hen required, the lyophilized ***liposomes*** are reconstituted in 0.9% saline." (emphasis supplied). It does not state that the addition of saline forms the lipid bilayers, it states that the lipid bilayers are already formed when the saline is added. Hence, contrary to the Examiner's statements, the Appellants' specification teaches that the lipid bilayers are formed during lyophilization, prior to the addition of the aqueous saline. Thus, water present in the t-

butanol is incorporated into the lipid bilayer formed during lyophilization, and the subsequent addition of saline merely forms the interior of the liposomes.

The Answer next posits that the claim language used in claim 138 does not distinguish between liposomes prepared using water in the organic alcohol + lipids as compared to water used in the saline resuspension step. Answer, page 5, middle of page. Curiously, this is the first time the Examiner has made such an argument, even in light of numerous, previous arguments made by Appellants that the claims ***do*** refer to water ***in*** the lipid bilayer. In any event, we disagree: Claim 138 references the drug 4-HPR "encapsulated" in a lipid material, wherein "***the lipid material*** comprises dimyristoyl phosphotidylcholine (DMPC) and water." Thus, in claim 138 it is NOT the interior of the liposome that comprises the water, it is the lipid material that comprises the water. The Examiner has failed to demonstrate that merely resuspending already formed liposomes in aqueous saline results in the introduction of water into the lipid bilayer itself as opposed to merely introducing water into the interior cavity that the lipid bilayer encapsulates.

Claims 139-140

The Examiner's argument with respect to dependent claims 139 and 140 is not entirely understood. Again, it is noted that the final rejection does not even attempt to make out a *prima facie* rejection of claims 139 and 140. In his Answer, the Examiner merely states that "[t]he amount of aqueous medium added therefore depends upon the mode of administration ...". Answer, bottom of page 5. However, the Examiner again appears to be referring to the aqueous medium and not the claim language which states that the water is *in* the lipid composition at the designated concentrations. Certainly these unsupported "throw-away" statements cannot constitute a *prima facie* case of obviousness when there is not a single reference that the

Examiner can point us to that teaches or suggests a 1 to 10% water content in the lipid bilayer itself as stated by the claims.

Moreover, once again for the first time in this prosecution, the Examiner states that claims 139 and 140 do not properly reflect the invention exemplified in Table 2, suggesting that Appellants should have claimed its invention as a process or product-by-process. Had the Examiner raised this issue prior to the Answer, Appellants might well have been willing to conform the language in a manner suitable to the Examiner. However, we would note at this juncture that the claim language specifically reflects the label contained in Table 2, which references at the left-hand column that the "Composition of liposome" has the various percentages of water, *etc.*

Lastly, and once again for the first time, the Examiner states that the data in Table 2 is not a proper comparison since the "t-butanol + no water" column employed a 1:17 w/w ratio of 4-HPR:Lipid, whereas the "t-butanol + water" column employed other ratios of 4-HPR:Lipid.

In response, had the Examiner raised this issue during active prosecution the Appellants would have been pleased to provide an explanation. Here, Appellants understand that the inventors believed it important for comparative purposes to include a slight additional amount of lipid where no water was included in the lipid bilayer, to sterically compensate for the absence of water. Thus, in the case of "no water" liposomes, the ratio of 1:17 (w/w) was used, whereas in the case of "water containing" liposomes, the ratios of 1:10, 1:5 and 1:15 were used. Notably, the absolute highest incorporation, 96.4%, was in connection with the 1:15 (w/w), as compared to the mere 60% incorporation in the case of the "no water" liposomes having a very similar 1:17 (w/w) ratio.

Claim 141

Claim 141 states that each of DMPC, soybean oil AND water are present in the lipid material of the liposome. With respect to the present rejection over Mehta in view of Ulukaya, no attempt has been made by the Examiner to address Appellants' arguments of separate patentability.

Here, Appellants again note that the Examiner has not pointed to any teaching wherein *water* is included in the lipid component along with soybean oil and DMPC, as referenced in claim 141, and thus has failed to make out a *prima facie* rejection.

Combinability with Secondary References

Appellants disagree with the Examiner's Answer with regard to the combinability of the secondary references, and will rely on the opening brief in this regard on appeal and at Oral Argument.

Secondary Considerations

Even if the Board concludes that a *prima facie* obviousness case has been made out, it is submitted that Appellants have presented strong evidence that the inclusion of water in the lipid bilayer along with the DMPC (claims 138-140) or with the DMPC + soybean oil (claim 141) exhibits a surprising and unexpected encapsulation efficiency as compared to DMPC without water or DMPC + soybean oil without water.

The Answer does not specifically address Appellants secondary considerations argument as such, but does question for the first time the lack of statistical evaluation, and, as noted briefly above, the different ratio of 4-HPR:Lipid used for the "minus water" as compared to the "plus water" studies in Table 2. Again, had the Examiner raised such questions in prosecution we might well have been able to address them to his satisfaction. In any event, with respect to the

difference in molar ratios of 4-HPR:Lipid in the "water-containing" as compared to the "non-water-containing" samples we would again point out that this was done to compensate for the presence of water to keep molar ratios of DMPC to drug similar.

With respect to the Answer's newly-presented "statistical evaluation" argument, Appellants can respond by noting that six different experimental studies with six different ratios of water to DMPC to drug and, in each case, the encapsulation efficiency was far superior to liposomes prepared in the absence of water.

With respect to the Answer's implication, at page 6, line 7, that Appellants' encapsulation efficiencies are not superior to Mehta's teaching of efficiencies up to 90.7 percent (Table 1 of Mehta), Appellants would observe the following:

- The proper comparison to demonstrate the importance of including water in the lipid component is to compare "4-HPR+lipid" to "4-HPR+lipid+water", which Appellants have done and shown dramatic improvement with that one little change of including water, holding everything else essentially constant.
- Notably, the highest encapsulation efficiency, 96.4%, was achieved using a 1:15:10 ratio of 4-HPR:lipid:water, as compared to a mere 60% efficiency using a similar 1:17 ratio of 4-HPR:lipid (no water).
- In Table 1, Mehta achieves encapsulation efficiencies up to 90.7% only using the very expensive composition of DMPC and DMPG, two separate and expensive *synthetic* phospholipids, while the present invention achieves similar encapsulation using only one synthetic phospholipid and water, and optionally soybean oil.

- Moreover, Table 1 of Mehta is really the wrong comparison in that that Table involves the encapsulation of retinoic acid, not 4-HPR. Again, the correct comparison is found in Table 2 of the present specification which compares the encapsulation efficiency of the closest-prior-art Mehta *technique* (using only DMPC + soybean oil with no water) to that embraced by the present claim (using DMPC + water or DMPC + soybean oil + water).

Appellants have provided arguments that address the comments raised in the Answer. Appellants respectfully submit that the Final Official Action's conclusions that the claims should be rejected are unwarranted. It is therefore again requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

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